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# Mathematical Biophysics

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## SOME GENERAL THEOREMS ON THE MOTION OF INCOMPRESSIBLE VISCOUS FLUIDS

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Some standard theorems about the motion of single fluids are reviewed and extended to the case of several fluids moving through each other. Some further results are obtained which do not have a counterpart in the case of a single fluid.

The mechanics of viscous fluids is of importance in the study of biological movements, diffusion processes, etc. The purpose of the present paper is to collect together some results of a more or less general nature, without entering into any detail as to actual solution of the equations of motion.

### *Single Fluid*

1. An incompressible fluid\* can move without viscous dissipation of energy only if it moves as a whole like a rigid body (Lamb, p. 549). Therefore if it is constrained to have zero velocity over a fixed finite area of surface it cannot move at all without dissipating energy into heat.

2. The energy equation for a fluid confined within a fixed boundary† at which it has zero velocity is

$$\frac{dK}{dt} = -f + \iiint V \cdot X \, d\tau; \quad (1)$$

where  $V = (u, v, w)$  is the velocity of the fluid;  $X = (X, Y, Z)$  is the field force acting on unit volume of fluid;  $d\tau$  denotes the element of volume, the integration being throughout the entire region in question;  $K$  is the total kinetic energy of the fluid in the region; and  $f$  is the dissipation. The quantity  $f$  is inherently positive, and can vanish only if the fluid is at rest throughout the region. Equation (1) is perhaps sufficiently obvious, but it may be derived by multiplying the

\* More exactly, a connected mass of such a fluid. Two separate portions of fluid can, of course, move relatively to each other without dissipation.

† Here, as throughout, the boundary may consist of one or more internal closed surfaces in addition to the external one; i.e. the region it bounds may be *periphractic* (Lamb, p. 38).



first three equations of (5) below by  $u$ ,  $v$ ,  $w$  respectively, and then adding, integrating, and transforming suitably (Lamb, p. 8).

If the volume forces have at each instant a potential,  $X(t) = -\nabla \Omega(t)$ , the last term drops out\* leaving simply

$$\frac{dK}{dt} = -f. \quad (2)$$

Thus under the operation of potential forces there is a unique steady state, namely that wherein the fluid is at rest throughout the region. This is furthermore a stable state, since any imported motion dies out to zero by dissipating its kinetic energy into heat. The steady state attained is independent of the force field  $X$ , provided that at each instant it has a potential  $\Omega$ . The dissipation in the steady motion is less than in any other motion having the same boundary velocities.

3. For a specified motion,  $K$  in (2) is proportional to the fluid density  $\rho$ , while  $f$  is proportional to the viscosity coefficient  $\eta$ . Thus it is seen that the rate at which the motion dies out increases with increasing  $\mu = \eta/\rho$ . Some idea of this may be gained by supposing that the velocity components were to die out uniformly throughout the region, i.e.  $u = u_0 \gamma(t)$ , etc. Then  $K$  and  $f$  both vary as  $\gamma^2$ , and upon integrating (2) we obtain

$$\gamma = e^{-\alpha \mu t}, \quad (3)$$

where  $\alpha > 0$  depends only upon the initial velocities and is homogeneous of degree zero in them. Thus  $\mu$  plays somewhat the role of an exponential decay factor. It was termed by Maxwell the *kinematical viscosity*.

4. Next consider the case where non-zero velocities for the fluid are prescribed over the boundary of a *moving* region. These boundary velocities are not entirely arbitrary, since the fluid motion must at each instant satisfy the equation of continuity  $\nabla \cdot V = 0$  throughout the region. This requires that the relation

$$\iint V \cdot ds = 0 \quad (4)$$

be satisfied identically on the moving boundary. Apart from this restriction the boundary velocities of the fluid may be assigned arbitrarily as functions of time.

5. The complete equations of motion of an incompressible fluid are

\* By transforming to a surface integral over the boundary,  
 $\iiint V \cdot X \, d\tau = - \iint \Omega V \cdot ds$ ,  
 and remembering that  $V = 0$  on the boundary.

$$\begin{aligned}
 \frac{\partial p}{\partial x} - X &= \eta \nabla^2 u - \rho \frac{Du}{Dt} \\
 \frac{\partial p}{\partial y} - Y &= \eta \nabla^2 v - \rho \frac{Dv}{Dt} \\
 \frac{\partial p}{\partial z} - Z &= \eta \nabla^2 w - \rho \frac{Dw}{Dt} \\
 \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} &= 0 ;
 \end{aligned}
 \tag{5}$$

where  $p$  is the mean pressure of the fluid (Lamb, p. 543), and

$$\frac{Du}{Dt} = \frac{\partial u}{\partial t} + \mathbf{V} \cdot \nabla u \tag{6}$$

etc.

Not much progress can be made with these equations in general. For slow motions, however, there are results corresponding to those of section 2. If a given motion has its velocities multiplied by  $\varepsilon$  then all the terms on the right side of (5) vary as  $\varepsilon$  except those in  $\mathbf{V} \cdot \nabla u$  etc. which vary as  $\varepsilon^2$ . Thus as  $\varepsilon$  decreases the latter become of less and less importance, and in the limit  $\varepsilon = 0$ , we have the so-called equations of slow motion:

$$\begin{aligned}
 \frac{\partial p}{\partial x} - X &= \eta \nabla^2 u - \rho \frac{\partial u}{\partial t} \\
 \frac{\partial p}{\partial y} - Y &= \eta \nabla^2 v - \rho \frac{\partial v}{\partial t} \\
 \frac{\partial p}{\partial z} - Z &= \eta \nabla^2 w - \rho \frac{\partial w}{\partial t} \\
 \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} &= 0 .
 \end{aligned}
 \tag{7}$$

6. Let  $(u, v, w)$  be one fluid motion, and let  $(u'' = u + u', v'' = v + v', w'' = w + w')$  be any other motion maintaining the same velocities on the boundary. Each set of velocity components defines a non-negative kinetic energy and a non-negative dissipation. In general,  $K'' \neq K' + K$  and  $f'' \neq f' + f$ . In fact (Korteweg, 1883; Lamb, p. 584) the instantaneous dissipations are related by

$$f'' = f + f' - 2\eta \iiint (u' \nabla^2 u + v' \nabla^2 v + w' \nabla^2 w) d\tau . \tag{8}$$



Consider two motions satisfying (7) and taking place under the action of force fields  $X_1$  and  $X_2$ . By using (8) twice with first one and then the other as the unprimed motion we obtain an equation which may be written\* as

$$\frac{dK'}{dt} = -f' + \iiint V' \cdot X' d\tau; \quad (9)$$

where  $V' = V_2 - V_1$ ,  $X' = X_2 - X_1$ , and the left side is the total rate of change of  $K'$  within the moving boundary.

If the difference force field  $X'$  derives at each instant from a potential this reduces to

$$\frac{dK'}{dt} = -f', \quad (10)$$

corresponding to (2).

Two force fields will be said to be *equivalent* if, within the moving region in question, their difference has at each instant a potential. The set of all force fields equivalent to a given one is the *equivalence class* of that force field.

Then from (10) it is seen that any two slow motions maintaining the same (time variable) velocities over the same (moving) boundary, and taking place under the action of equivalent force fields, tend to become ultimately identical regardless of different initial conditions. If at some instant the two motions are identical they will remain so thereafter, since  $K'$  can change only by decreasing and it is already at its minimum value of zero. It follows that a slow motion is uniquely determined by its initial and boundary velocities and the equivalence class of its force field.

7. Equation (10) for the decay of the difference motion is quite the same as (2), and the remarks of section 3 apply. Thus the rate at which the initial conditions die out in a fluid motion increases with increasing  $\mu$ . If after a certain instant two motions have equivalent force fields and the same boundary velocities, they tend to become identical at a rate which increases with increasing  $\mu$ . Thus with increasing  $\mu$  a motion depends less and less on its past history and be-

\* By an argument involving the fact that  $V'$  is always zero at the moving boundary, and that the total time derivative of an integral taken throughout a moving region is

$$\frac{d}{dt} \iiint h d\tau = \iiint \frac{\partial h}{\partial t} d\tau + \iint h W \cdot ds,$$

where  $W$  is the velocity of the moving boundary.



comes more and more nearly determined by the instantaneous boundary velocities and force class.

The limit of this trend is a motion which at each instant satisfies the equations obtained from (5) by omitting the terms in  $\rho$ , namely

$$\begin{aligned}\frac{\partial p}{\partial x} - X &= \eta \nabla^2 u \\ \frac{\partial p}{\partial y} - Y &= \eta \nabla^2 v \\ \frac{\partial p}{\partial z} - Z &= \eta \nabla^2 w \\ \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} &= 0.\end{aligned}\tag{11}$$

For two motions satisfying these equations and having equivalent force fields and the same boundary velocities the use of (8) twice gives simply  $f' = 0$ , so that the motions must be identical. It follows that a solution of (11) is uniquely determined by the boundary velocities and the class of the force field.

Let  $V$  be a motion satisfying (7), and let  $V_0 = V - V'$  be a motion with the same boundary velocities, and equivalent force field, and at each instant satisfying (11). Using (8) twice then gives

$$\frac{dK'}{dt} = -f' - \rho \iiint V' \cdot \frac{\partial V_0}{\partial t} d\tau.\tag{12}$$

If  $V$  satisfies (5) rather than (7) there are additional terms having a factor  $\rho$ .

As  $\rho/\eta$  goes to zero so does  $f'/\eta$  in (12). Thus with increasing  $\mu$  a motion tends to become identical with  $V_0$ , which depends only upon the instantaneous boundary velocities and force class.

8. It is obvious that there can be no steady motion in a fixed region unless the boundary velocities are maintained steady in time. From (5) it is seen that a further necessary condition for steady motion is that  $X - \partial p/\partial x$ , etc., be independent of time; i.e. that  $X$  be equivalent to a steady force field.

But if these conditions are satisfied  $V_0$  as defined above is steady and (12) reduces to

$$\frac{dK'}{dt} = -f',\tag{13}$$

so that a slow motion with assigned steady boundary velocities and

steady force class tends stably to a unique steady state. This follows otherwise from considerations given in section 10 below.

9. Let  $V_0$  be a slow, steady, potential-force motion and  $V$  be any other motion with the same boundary velocities. Then (8) gives

$$f = f_0 + f', \quad (14)$$

where  $V' = V - V_0$ . Thus the dissipation in slow, steady motion under the operation of forces having at each instant a potential is less than in any other motion having the same boundary velocities.

Some special motions satisfying the complete equations of motion (5) are known (Rayleigh, 1913; Lamb, p. 585) which also make the dissipation a minimum; in general, however, any actual motion will have a higher dissipation than the corresponding potential force solution of (11).

More generally (8) and (11) yield

$$f - 2 \iiint V \cdot X \, d\tau = f_0 - 2 \iiint V_0 \cdot X \, d\tau + f', \quad (15)$$

so that the excess of the dissipation over twice the rate at which the volume forces are doing work upon the fluid is less in slow steady motion than in any other motion having the same boundary velocities and the same force field.

10. From sections 8 and 9 it is seen that with steady boundary velocities and potential forces a slow motion tends to a steady state of minimum dissipation. It can be further shown that the dissipation decreases monotonically in this process.

For any motion with steady boundary velocities we have (Lamb, p. 585)

$$\frac{df}{dt} = -2\eta \iiint (\dot{u}\nabla^2 u + \dot{v}\nabla^2 v + \dot{w}\nabla^2 w) \, d\tau, \quad (16)$$

where the dots denote partial time derivatives. If the motion satisfies (7) with potential forces, this becomes

$$\frac{df}{dt} = -2\rho \iiint (\dot{u}^2 + \dot{v}^2 + \dot{w}^2) \, d\tau, \quad (17)$$

so that  $f$  continually decreases until the motion is steady.

More generally for a slow motion under forces equivalent to a steady field  $X$  the left side of (17) is replaced by  $\frac{d}{dt} (f - 2g)$ , where

$$g = \iiint V \cdot X \, d\tau. \quad (18)$$

This describes the monotonic decrease of the quantity which was shown in (15) to attain its minimum value in the steady state.



*Several Fluids*

11. In connection with diffusion processes it is appropriate (Young, 1938) to consider the motion of different fluids through each other, on the supposition that they exert frictional drag forces on each other whenever there is relative motion between them. Thus regarded, Fick's law describes the diffusion of a solute as the motion of an incompressible fluid whose inertial and viscous forces are neglected in comparison with the drag force exerted by the solvent.

To the extent to which the diffusion coefficient is constant, Fick's law makes the drag force between solvent and solute proportional to their relative velocities. This is an assumption that in one form or another has had considerable acceptance and support (Fletcher, 1911; Smoluchowski, 1916; Burger, 1918; Ehrenfest, 1918, Wiener, 1921; Weyssenhoff, 1925; Chapman, 1928; Young, 1938), and it will be made in what follows here. We suppose, therefore, that the volume drag force exerted by fluid  $j$  on fluid  $i$  is given by

$$\mathbf{F}_{ij} = k_{ij}(\mathbf{V}_j - \mathbf{V}_i), \quad (19)$$

where the  $k_{ij}$  are positive constants. For the mutual drag forces to be equal and opposite it is necessary that  $k_{ij} = k_{ji}$ . Note that when a solute is pictured as an incompressible fluid the velocity is proportional to the mass rate of flow, i.e. to what would ordinarily be denoted by the product of the density and the mean drift velocity of the solute particles. The total volume force on fluid  $i$  is

$$\sum_j \mathbf{F}_{ij} + \mathbf{X}_i, \quad (20)$$

where  $\mathbf{X}_i$  is the resultant of all other forces besides the drag forces. For convenience  $\mathbf{X}_i$  will be referred to as the external force on fluid  $i$ .

12. Using the total force (20) in equation (1) and summing for all the fluids gives the total energy equation for a region in which all fluids have zero boundary velocities; namely

$$\frac{d}{dt} \sum K_i = -F + \sum \iiint \mathbf{X}_i \cdot \mathbf{V}_i d\tau, \quad (21)$$

where

$$F = \sum f_i + \sum_i \sum_j \Phi_{ij} \quad (22)$$

$$\Phi_{ij} = \frac{1}{2} \iiint \mathbf{F}_{ij} \cdot (\mathbf{V}_j - \mathbf{V}_i) d\tau.$$

$F$  is the total dissipation within the system due to viscous and frictional drag forces. It is inherently positive, as is apparent from (19), and vanishes only when all the fluids are at rest. For this conclusion

it would have been sufficient to suppose merely that the scalar product under the integral in  $\Phi_{ij}$  is non-negative, instead of the more restrictive assumption (19). This, however, would not suffice for sections 13 and 15 below which assume (19) specifically.

If the external forces  $X_i$  have at each instant a potential, (21) reduces to

$$\frac{d}{dt} \sum K_i = -F. \quad (23)$$

This is analagous to (2), and shows that a system with zero boundary velocities and potential external force fields tends stably to a unique steady state of zero motion and minimum total dissipation  $F$ .

Writing out (5) for each component fluid shows that steady zero motion requires  $X_i = \partial p_i / \partial x$ , etc., so that the system can be at rest only if all the external force fields are equivalent to zero.

*Thus the slow motion of one or more incompressible fluids with relative drag forces as given by (19) is uniquely determined by the initial and boundary velocities and the equivalence classes of the external force fields. Two motions with different initial velocities but with identical boundary velocities and equivalent external force fields tend to become ultimately identical. If the boundary velocities and the equivalence class of the external force field are maintained steady in time then the motion tends stably to a unique steady state.*

13. Using the total force as given by (20) and (19) in (9) gives for the difference of two slow motions maintaining the same boundary velocities

$$\frac{d}{dt} \sum K'_i = -F' + \sum \int \int \int X'_i \cdot V'_i d\tau, \quad (24)$$

so that the conclusions of section 6 apply to a system of fluids moving through each other under the influence of drag forces (19), just as to the motion of a single fluid.

For slow motion with steady boundary velocities and potential external fields (16) gives

$$\frac{dF}{dt} = -2 \sum \rho_i \int \int \int (\dot{u}_i^2 + \dot{v}_i^2 + \dot{w}_i^2) d\tau; \quad (25)$$

or if the external fields are equivalent to steady fields, which is necessary for existence of a steady motion, the left side is replaced by  $\frac{d}{dt}(F - 2G)$  where  $G$  is the sum of  $g_i$  in (18). Thus the conclusion of section 10 also extends to the case of multiple fluids with drag forces as in (19).



14. The total stress system due to several moving fluids is the sum of the stress systems for each fluid, which in turn involve sums of the pressures  $p_i$  and space derivatives of  $\eta_i$  times the various velocity components (Lamb, p. 544). The total stress thus depends only upon the quantities

$$\begin{aligned} P &= \sum p_i \\ V &= \sum \eta_i V_i. \end{aligned} \tag{26}$$

Writing the equations of slow steady motion (11) for each fluid, using (20), and summing over the fluids gives

$$\begin{aligned} \frac{\partial P}{\partial x} - X &= \nabla^2 u \\ \frac{\partial P}{\partial y} - Y &= \nabla^2 v \\ \frac{\partial P}{\partial z} - Z &= \nabla^2 w \end{aligned} \tag{27}$$

$$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = 0,$$

where  $P$  and  $(u, v, w) = V$  are the quantities defined in (26), and  $X$  is the sum of the external force fields  $X_i$  of (20). But (27) describes the slow steady state motion of a single fluid under a force field  $X$ , which is determined by the boundary velocities. Hence the total stress can be found without determining the individual fluid velocities  $V_i$ . *In particular if  $X$  is equivalent to zero then the total stress is merely the sum of the stresses of each fluid in steady force-free motion in the absence of the other fluids and with its own boundary velocities.*

If all the fluids have the same kinematical viscosity  $\mu$  a corresponding result may be obtained from the time variable slow motion equations (7). This results in the addition of terms  $-(1/\mu)(\partial u/\partial t)$ , etc., on the right sides of the first three equations in (27), and reduces the calculation of the total stress in a varying multiple fluid system to that of a single fluid motion.

Note that the results of this article involve only the assumption that  $F_{ij} = -F_{ji}$ ; they do not depend upon (19).

15. Now suppose that one of the fluids (say No. 1) in a system is identically at rest. Assuming the specialized drag forces (19) and introducing the total force (20) into the complete equations of motion

(5) for a single fluid we see that this implies the equations

$$\begin{aligned}\frac{\partial p_1}{\partial x} - X_1 &= \sum_j k_{1j} u_j \\ \frac{\partial p_1}{\partial y} - Y_1 &= \sum_j k_{1j} v_j \\ \frac{\partial p_1}{\partial z} - Z_1 &= \sum_j k_{1j} w_j ,\end{aligned}\tag{28}$$

where  $X_1 = (X_1, Y_1, Z_1)$  is the external force acting on the stationary fluid. Differentiating and adding and remembering that  $\nabla \cdot V_j = 0$  for each fluid gives

$$\nabla^2 p_1 = \nabla \cdot X_1 .\tag{29}$$

If  $X_1$  has at each instant a potential (29) becomes

$$\nabla^2 P = 0 ,\tag{30}$$

where

$$P = p_1 + \Omega_1\tag{31}$$

$$X_1 = -\nabla \Omega_1 ;$$

while (28) becomes

$$V = \nabla P ,\tag{32}$$

where

$$V = \sum_j k_{1j} V_j .\tag{33}$$

But then  $P$  is determined by the value of its normal derivative over the boundary, i.e., by the normal components of the fluid velocities. The tangential velocities can not be assigned arbitrarily in addition without rendering (28) inconsistent. Hence a slight change in the boundary velocities of any of the other fluids can enforce motion on the part of fluid No. 1, and *except in special cases the motion of any fluid entails that of all the fluids*. A special case of this result has been noted previously (Young, 1940).

If  $X_1$  does not have a potential it is still seen from (29) that  $p_1$  is determined to within a harmonic function;

$$p_1 = \alpha + H ,\tag{34}$$

where  $\alpha$  is determined by  $X_1$  and  $H$  is an arbitrary harmonic. Then (28) becomes

$$V + X_1 - \nabla \alpha = \nabla H ,\tag{35}$$

and the argument goes through as before.



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## A NEURAL MECHANISM FOR DISCRIMINATION III: VISUALLY PERCEIVED LENGTHS AND DISTANCES

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A previously discussed neural mechanism for the discrimination of intensities is here applied to the judgment of visual lengths and distances on the assumption that the "intensity" associated with the magnitude being perceived is the intensity of innervation of the appropriate eye muscles necessary for scanning and fixating. Comparison with experimental data is made in the case of the judgment of lengths.

1. *The problem.* In previous papers (Householder 1939, 1940: these will be denoted hereafter by DI and DII.) a hypothetical neural mechanism was described which has the property of diverting to different neural pathways the nervous responses from stimuli of different intensities. Furthermore, from this mechanism as it was set up it was possible to deduce the form of the Weber function that would result (i.e. the function describing the stimulus which is "just noticeably greater" than a given stimulus) and so to compare this theoretical function with those obtained experimentally. Comparisons were made with empirical data taken from the literature for visual brightness, for loudness, for tactile pressures, and for lifted weights. For the first three types of data the intensity of the stimulus  $S$  acting upon the mechanism proper was supposed proportional to the intensity of the peripheral stimulus whereas for lifted weights account was taken of the probable effect of the muscle receptors in transmitting the stimulus.

In the present investigation we wish to consider how the same type of mechanism might operate in the making of judgments on spatial magnitudes visually perceived. Inasmuch as the mechanism assumes that stimuli of graded *intensity* are applied, it is necessary to tell what physiological intensities are supposed to yield the experience of the *extension* of the stimulus-object, for only if this is possible will the mechanism in question be applicable, and the derivation of the associated Weber function be legitimate. Before doing this, however, it is convenient to introduce an approximation to the basic formula derived in DI, which gives the Weber function in terms of the intensity acting upon the mechanism itself.

2. *An approximation.* If  $u$  is proportional to the intensity of the stimulus acting upon the mechanism and if  $u$  and  $u(1+\delta)$  are the intensities corresponding to "just discriminably different" peripheral stimuli, then according to equations (16), (22), and (23) from DI

$$\begin{aligned} uz^3 - 2(x+1)z - (x+1)^2 &= 0 \\ ux^3 + x^2 - 1 &= 0 \\ x + z &= \delta \end{aligned} \quad (1)$$

where  $x$  and  $z$  are auxiliary variables. The solution giving  $\delta$  as a function of  $u$  can actually be obtained in closed form; this was done in DI, and it was further shown that  $\delta$  is monotonically decreasing from  $\infty$  for  $u = 0$  to 0 for  $u = \infty$ . Nevertheless, this closed solution is too complex and unmanageable. It is simpler to obtain  $u$  and  $\delta$  as functions of a single parameter, and from this parametric representation a much simpler but still adequate approximate expression is readily derived.

From the second of equations (1) we have

$$u = \frac{1 - x^2}{x^3}. \quad (2)$$

Hence if we set this expression for  $u$  and substitute

$$z = xy$$

into the first of these equations we obtain an equation which readily simplifies to the form

$$(1 - x)y^3 - 2xy - (x+1) = 0,$$

after suppressing a factor  $x+1$  which is necessarily positive. From this we have

$$x = \frac{y^3 - 1}{y^3 + 2y + 1}. \quad (3)$$

Evidently

$$\delta = x(1 + y),$$

or

$$\delta = \frac{(y+1)(y^3-1)}{y^3+2y+1}. \quad (4)$$

Thus if we substitute the expression (3) for  $x$  into (2) we have

$$u = \frac{4y(y+1)(y^2+1)(y^3+2y+1)}{(y^3-1)^3}, \quad (5)$$

and (4) and (5) together constitute a parametric representation as desired.

However we note that  $\delta$  is monotonically increasing and  $u$  monotonically decreasing in  $y$ , and that the range of  $y$  for which  $u$  and  $\delta$  are positive, and hence meaningful, is from  $y = 1$  to  $y = \infty$ . (The proof of this statement is contained in the ensuing discussion.) It is more convenient therefore, to introduce the new parameter  $t$ , where

$$y = \frac{t+1}{t}, \quad (6)$$

so that  $u$  is monotonically increasing,  $\delta$  monotonically decreasing in  $t$ , and the range of  $t$  is from  $t = 0$  to  $t = \infty$ . This gives

$$u = \frac{4t^2(t+1)(2t+1)(2t^2+2t+1)(4t^3+5t^2+3t+1)}{(3t^2+3t+1)^3}, \quad (7)$$

$$\delta = \frac{(2t+1)(3t^2+3t+1)}{t(4t^3+5t^2+3t+1)}.$$

Let us make the substitutions

$$\eta = \log \delta, \quad \xi = \log u. \quad (8)$$

Then we find

$$\begin{aligned} d\eta/dt &= -(24t^6 + 72t^5 + 87t^4 + 54t^3 + 21t^2 + 6t + 1) / \\ &\quad [t(2t+1)(3t^2+3t+1)(4t^3+5t^2+3t+1)], \\ d\xi/dt &= (144t^9 + 648t^8 + 1350t^7 + 1704t^6 + 1443t^5 + 858t^4 \\ &\quad + 363t^3 + 108t^2 + 21t + 2) / [t(t+1)(2t+1)(2t^2+2t+1) \\ &\quad \times (3t^2+3t+1)(4t^3+5t^2+3t+1)]. \end{aligned}$$

The monotonicity of  $\xi$  and  $\eta$ , and hence of  $u$  and  $\delta$  as asserted above, is evident from these two formulas. From these we find by dividing that

$$\begin{aligned} d\eta/d\xi &= -(48t^9 + 240t^8 + 534t^7 + 696t^6 + 591t^5 + 345t^4 + 143t^3 \\ &\quad + 43t^2 + 9t + 1) / (144t^9 + 648t^8 + 1350t^7 + 1704t^6 \\ &\quad + 1443t^5 + 858t^4 + 363t^3 + 108t^2 + 21t + 2) \\ &= 1/(2 + tT_1) = -(1 + T_2)/3, \end{aligned} \quad (9)$$

where

$$\begin{aligned} T_1 &= (48t^8 + 168t^7 + 282t^6 + 312t^5 + 261t^4 + 168t^3 + 77t^2 + 22t + 3) / \\ &\quad (48t^9 + 240t^8 + 534t^7 + 696t^6 + 591t^5 + 345t^4 \end{aligned}$$



$$+ 143t^3 + 43t^2 + 9t + 1)$$

and

$$T_2 = (72t^8 + 252t^7 + 384t^6 + 330t^5 + 177t^4 + 66t^3 + 21t^2 + 6t + 1) / \\ (144t^9 + 648t^8 + 1350t^7 + 1704t^6 + 1443t^5 + 858t^4 \\ + 363t^3 + 108t^2 + 21t + 2).$$

Since  $T_1$  and  $T_2$  are always positive when  $t$  is positive, it is evident that

$$-1/2 \leq d\eta/d\xi \leq -1/3, \quad (10)$$

and that this derivative takes the extreme values  $-1/2$  and  $-1/3$  only when  $t = 0$  and when  $t = \infty$ , respectively. Because of the slight variation in the value of this derivative,  $\eta$  can be represented with good approximation over a finite range as a linear function of  $\xi$ , and hence  $\delta$  can be represented as proportional to a power of  $u$  over this same range. The representation can be determined by taking the first term in the Taylor series expansion of  $\eta - \eta_0$  in powers of  $\xi - \xi_0$ , for some  $\xi_0$  and  $\eta_0$ , or, perhaps better, by taking the linear interpolation formula determined by some two points  $(\xi_0, \eta_0)$  and  $(\xi_1, \eta_1)$ . The calculations can be made most conveniently from the simpler expressions (4) and (5) in terms of  $y$ .

In any case, we have, for the approximate representation of  $\delta$  as a function of  $u$  the expression

$$\delta = \beta u^{-\alpha} \quad (11)$$

where  $\beta$  and  $\alpha$  are to be determined according to the range over which the approximation is required, and where

$$\frac{1}{3} \leq \alpha \leq \frac{1}{2}. \quad (12)$$

At this point we may point out the similarity of the form (11) to the psychophysical law of Cattell and the generalizations thereof (Woodworth, 1914; Guilford, 1932). It is true that  $u$  is not supposed to be the intensity of the peripheral stimulus, but to be the amount of the excitatory "factor", i.e. the intensity of the stimulus, which is acting upon the central discrimination mechanism itself. Nevertheless it may not be too unreasonable to suppose that this central intensity is roughly proportional to the peripheral intensity for at least some sense modalities, in which case equation (11) can be used directly with  $u$  as the peripheral intensity. This was done in the paper DI for visual brightness, for loudness, and for pressure.

It should be noted further that  $\alpha$  and  $\beta$  are *not* independent para-

meters, and that the only variable parameter actually involved in formula (11) is the factor of proportionality contained in the variable  $u$ .

3. *Visual lengths*. It has been remarked above that if the theory of intensity discrimination is to be applicable to the discrimination of visually perceived magnitudes, then we must suppose the experience of extension to be due to some stimulus whose gradations in intensity correspond to the magnitude of the extension. This physiological intensity of stimulation must be supposed to underly and to result in the psychological experience of extension in space.

This physiological intensity we shall assume to be associated with the extrinsic eye-muscles. In view of the known distribution of the rods and cones on the retina (Hecht, 1938), it does not seem reasonable that the required intensity should be due to a summation of the responses resulting from stimulation of these elements, though this would be otherwise the most natural assumption to make. The question of whether the experience of spatial extension in visual perception can be attributed to the role of the eye-muscles has been much discussed in qualitative and philosophical terms, and we do not need to go into this here (see, e.g., Baird, 1903; Roelofs, 1935, among others). In this connection we might mention however, some work of Kennard's (1939) in which lesions in the motor cortex in monkeys led to visual disturbances. It is of interest to note, also, that Mach (1861) formulated a quantitative theory for the discrimination of visually perceived lengths and angles based on the assumption that the experience of extension derives from the action of the eye-muscles.

Recently Rashevsky (1938b, 1940) developed a theory of the perception of visual forms based on such an assumption. As he points out, it cannot be the *actual* movements of the eye that are responsible for the experience of the extension, or for the perception of the form, since it is known that the eye does not in fact, or at least need not, accurately scan the outlines of the form being perceived. But we may assume that the actual movements of the eyes are the resultants of innervations from various centers, one of which, if the others were inactive, would cause the eye actually to scan the object. This is the center  $C_s$  in Figure 1, taken from the above mentioned papers.

Suppose, now, that there is presented for visual perception a single straight-line segment, placed in the horizontal plane of the two eyes. For simplicity we consider only one eye. Suppose the segment is so placed that one endpoint can be fixated when the eye is in the primary position, the segment and the line of sight being then at right angles. The innervation from the center  $C_s$  is then supposed to be such that it tends to cause the eye to rotate so as to fixate the other endpoint of the segment. The center  $C_s$  is supposed to be connected

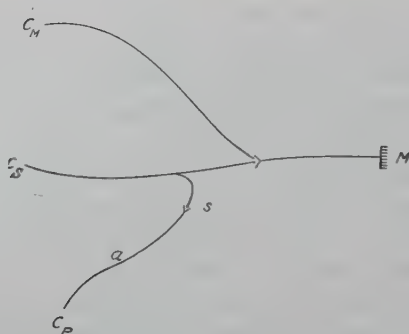


FIGURE 1

with a discriminating mechanism of the type discussed in DI, so that the intensity  $S$ , or  $u$  delivered to this mechanism is proportional to the intensity of the innervation from  $C_S$ .

Since the segment is supposed to be horizontal, the rotation of the eye, if  $C_S$  alone were acting, would be in the horizontal plane, and only the action of the horizontal rectus muscles need be considered. For vertical, and certainly for oblique, rotations the situation is somewhat more complicated since more than one pair of muscles is involved. In the present case the linear contraction of the appropriate, lateral or medial, rectus muscle is proportional to the angular rotation of the bulbus. It may be that the relative, rather than the linear, contraction of the muscle should be considered, but the difference could amount, at most, to a change of a few per cent in the Weber ratio for longer segments.

If  $S$  is the amount of  $\varepsilon - j$  produced at the synapse as a result of the activity of  $C_S$ , and if  $\bar{S}$  is the amount produced as a result of the activity of  $C_M$ , then  $S + \bar{S}$  is the total amount acting on the fibers leading to the muscles, and  $S$  is the amount acting on the fibers leading to the discrimination mechanism. The relation between the actual contraction of the muscle fibers and the quantity  $S$ , when  $\bar{S} = 0$ , depends, in part, upon the number of stages in the sequence of fibers between this and the muscle fibers themselves; likewise the relation between  $S$  and the measure  $u$  of  $\varepsilon - j$  acting upon the discrimination mechanism depends upon the number of stages in this intervening sequence. If  $E$  represents the intensity of excitation of a nerve fiber (see Rashevsky 1938a or 1940 for a definition of this term), or if it represents the linear contraction of the muscle, and  $S$  the amount of  $\varepsilon - j$  acting upon it, we assume that in either case  $E$  is the same function of  $S$ , and hence if the same number of synapses intervene in the sequence between  $C_S$  and the muscle as between  $C_S$  and the mechan-



ism, then we may suppose that the actual rotations of the bulbus is given by

$$\theta = \lambda(S + \bar{S}), \quad (13)$$

with, now,  $S$  proportional to  $u$ .

If the centers  $C_S$  and  $C_M$  are completely independent, then for scanning a segment which subtends an angle  $\theta$ ,  $S$  should be given by (13) with  $\bar{S} = 0$ . But if these are not completely independent,  $S$  should be given by (13) with  $\bar{S}$  taken as some non-zero, positive or negative quantity. This may be thought of as corresponding to a certain average contribution of the center  $C_M$ . No suggestion is made here as to the precise manner in which such an interconnection might occur, but certainly the fact that different centers mutually affect one another is too well known to require discussion. Neither do we suggest a mechanism for the center  $C_S$  itself, though it seems reasonable to suppose that its operation depends in some fashion upon conditioning.

Instead of (13), various other forms might be suggested and would be *a priori* possible. If the sequence to the muscles is the longer sequence,  $\theta$  should be a function of  $u$  which is concave downward; if the reverse it should be concave upward. The relation (13) may be regarded as a first approximation to either one, and in the absence of anatomical evidence, one should be able to decide between the two cases by an adequate series of discrimination measurements.

If we assume (13), then, we have

$$u = \gamma(\theta - \theta_0), \quad (14)$$

by an obvious change of parameter, since  $u$  is proportional to  $S$ . Hence from (11)

$$u + \delta u = u + \beta u^{1-\alpha} = \gamma(\theta + \Delta\theta - \theta_0),$$

where  $\Delta$  is the Weber ratio measured in terms of the angles subtended by the discriminated lengths. Hence, after making a further change of parameter,

$$\Delta\theta = \kappa(\theta - \theta_0)^{1-\alpha}. \quad (15)$$

In this equation there are two parameters,  $\kappa$  and  $\theta_0$ . The term  $\alpha$  in the exponent is not a parameter, as was noted above, but has the value that enables us to approximate to the function  $\delta(u)$ , over the range covered, by an expression of the form (11).

This equation (15) has been compared with the experimental results of Chodin (1877) as shown in Figure 2, where the points repre-

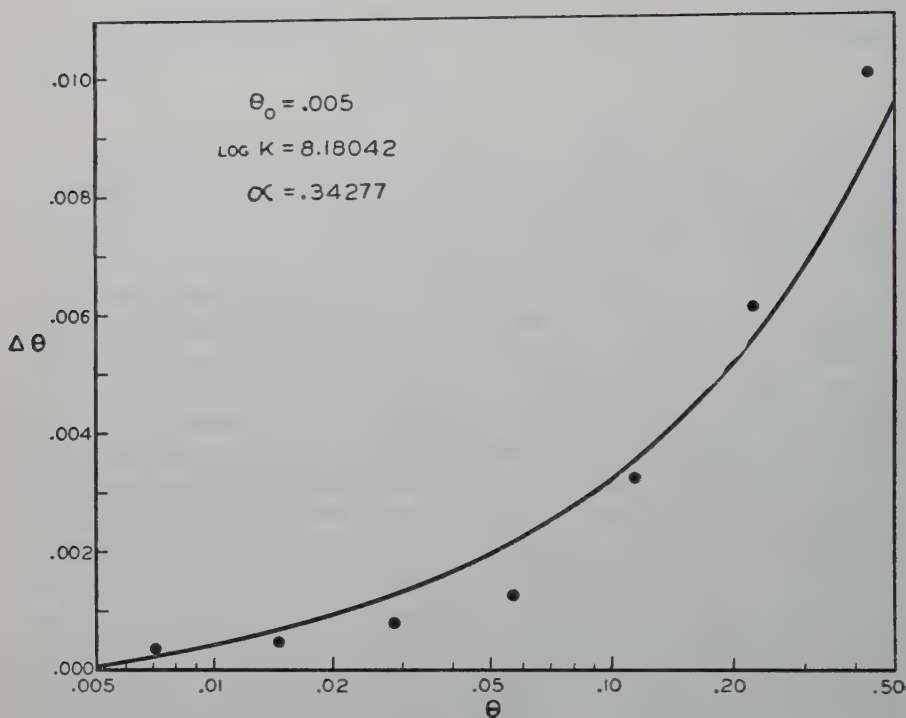


FIGURE 2

sent experimental values, and the curve is the graph of equation (15). Chodin laid the segments to be compared end-to-end (whence our assumption that one end-point was to be fixated by the eye in the primary position), and obtained J.N.D.'s for lengths of 2.5, 5, 10, 20, 40, 80 and 160 mm. at a distance of 350 mm. He ran two series of experiments, and we have taken, for our comparison, the means of these two sets of results. The values of the parameters and of  $\alpha$  are given on the graph.

For very short lengths the mechanism necessarily breaks down, since according to (15),  $\Delta$  would have to be zero for  $\theta = \theta_0$ , which is obviously absurd. It is not to be supposed that objects whose retinal images are of the order of the diameter of the fovea should be judged by means of the same mechanism. Quite possibly a summation of retinal stimulation may be involved for such magnitudes.

Moreover, for longer segments the assumption that the horizontal rectus muscles are alone acting becomes less accurate, and deviations are to be expected here. Whether their activity should "confuse" the judgment and make the ratio larger, or should "sharpen" it, would be a question to be decided empirically, and the mechanism

would require further elaboration accordingly. It may, indeed, be noted that if one attempts to fit only the first four points (for the four shorter lengths), the parameters can be chosen to give a very accurate representation, in which case, however, the empirical Weber ratio for the three longer segments are considerably greater than the predicted values. This seems to indicate some kind of a "confusion", rendering the discrimination less fine. But if one supposes that  $\bar{S}$  is an increasing function of the innervation to these other muscles then this is precisely what one should expect.

4. *Binocular distance judgments.* In the judgment of distance (from subject to object) in a given situation, obviously a variety of cues is possible and any one or any combination of these might actually be employed. However, one of these must be due to the degree of convergence of the eyes, or to the disparity of the retinal images of the object, when this is seen with both eyes. Evidently accommodation also plays a part, and the relative importance of these two factors might well vary from individual to individual (Carr and Allen, 1906) and also from situation to situation.

Suppose that, by some means, accommodation cues, size cues, shadings and the like can be eliminated, and the subject is required to compare the distances of two objects, successively presented, when no cues are possible except the degrees of convergence. We shall suppose that fusion of the images is accomplished in every case, though this assumption is not necessary if we suppose that, as with the previous mechanism, the innervation from a certain  $C_s$  produces the  $u$ , rather than the actual fusional movements themselves. Presumably  $u$  should be zero when the eyes are in the primary position, and should increase as the angle between the visual lines for the two eyes increases. The simplest assumption would be that  $u$  is simply proportional to this angle  $2\theta$ . On the other hand, however, it is impossible to converge the eyes beyond a certain maximal angle, whence a more plausible assumption would be that  $u$  becomes infinite for some value of  $\theta$  which is less than, or at most equal to  $\pi/2$ . The simplest function of this type is

$$u = \gamma \theta / (\theta_0 - \theta) . \quad (16)$$

However, if we suppose that  $\theta_0 = \pi/2$  and that convergence is possible only up a certain maximal value of  $u$ , then we may write

$$u = \gamma \tan \theta \quad (17)$$

as a function very closely approximating to (16). This, however, does not deviate appreciably from the linearity assumption, since the graph



of the tangent can be fairly closely approximated by a straight line for angles up to about  $\pi/4$ , which is close to the maximal convergence possible.

If we consider (17), and if  $2a$  is the distance between the eyes, and  $x$  the distance to the object, then evidently

$$a/x = \tan \theta = u/\gamma, \quad (18)$$

whence  $u$  is inversely proportional to the distance. In this case we may take the inverse of the distance as the measure of the physiological intensity, and the theoretical Weber ratio so measured is given by the function  $\delta(u)$ . The only parameter involved is the parameter  $\gamma a$ .

If the form (16) is assumed,  $\Delta$  can be calculated as a function of  $\theta$  from the approximation (11), but it is perhaps simpler to calculate the empirical  $u/\gamma$  and  $(1 + \delta) u/\gamma$  from (16), from which  $\delta$  can be obtained and compared with the theoretical curve. Here an additional parameter  $\theta_0$  is introduced. Experiments are now being conducted for the purpose of obtaining a series of empirical measurements for testing the above formulation.

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DEFORMATION OF SHELL-SHAPED CELLULAR AGGREGATES: APPLICATION TO GASTRULATION

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An equation derived in a previous paper is integrated, and applied to the theory of invagination of a gastrula. Comparison with experimental data is made.

In a previous paper (Rashevsky, 1940 b) we have derived the following equation for the deformation of a cellular shell:

$$\frac{1}{r'} \frac{dr'}{dt} = - \frac{pr}{4\delta\eta} . \tag{1}$$

The notations used here are the same as in *loc. cit.* We shall first study the above equation for the case of a constant  $p$ , assuming that during the process of closure the shell remains spherical. Such a case will arise when the cells of the aggregate have a constant polarity (Rashevsky, 1940 a).

Referring to Figure 1, we have again, as in *loc cit.*, the relations:

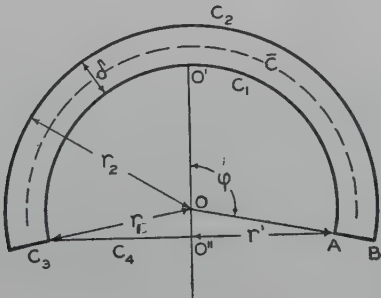


FIGURE 1

$$V = 2\pi r^2 (1 - \cos \phi) \delta ; \quad r' = r \sin \phi . \tag{2}$$

Expressing (1) the quantities  $r$  and  $r'$  in terms of  $\phi$  and  $V$ , and putting

$$p \sqrt{\frac{V}{8\pi\delta^3\eta^2}} = A , \tag{3}$$

we obtain from equation (1):

$$\frac{d\phi}{dt} = \frac{A \sin \phi}{(1 - \cos \phi)^{3/2}}. \quad (4)$$

Introducing

$$x = \frac{\phi}{2} \quad (5)$$

and separating the variables, we find

$$\frac{\sin^2 x \, dx}{\cos x} = B \, dt; \quad B = A/2^{3/2}. \quad (6)$$

Integrating, we find:

$$-\sin x + \frac{1}{2} \log \frac{1 + \sin x}{1 - \sin x} = Bt + C, \quad (7)$$

where  $C$  is an integration constant.

The next case which we investigate is that of a polarization varying in the manner discussed previously (Rashevsky, 1940 b). To this end we should introduce equation (8) of *loc. cit.* into equation (10) of *loc. cit.* and then the latter into equation (11). The expression for  $p$  thus obtained should then be introduced into equation (1) of the present paper. Such a procedure however leads to very clumsy expressions which cannot be handled analytically. We therefore use a different approximation method from the one used in *loc. cit.* in order to obtain the desired result.

Consider first a completely closed spherical shell, whose thickness  $\delta$  is small as compared with its radius  $r$ . We may calculate the difference  $c_2 - c_1$  in that case by remembering that the amount  $4\pi r^2 \delta q$  of substance consumed in the shell per second is equal to the amount flowing in. The average amount flowing radially through the shell is equal to  $4\pi r^2 (c_2 - c_1) D_i / \delta$ . Since at the inner surface of the shell the radial flow is zero, therefore the maximum flow inward at the outer surface is  $8\pi r^2 (c_2 - c_1) D_i / \delta$ . Equating this amount to that consumed, we find:

$$c_2 - c_1 = \frac{q\delta^2}{2D_i}. \quad (8)$$

An expression of the same form, except for a difference of the numerical factor is obtained by introducing equation (8) of *loc. cit.* into equation (10) of *loc. cit.* after putting in both of them  $s_1 = 0$ ,  $s_2 = 2$ , which corresponds to a closed shell.

Consider again a completely closed shell, in which, however, one part is characterized by a rate of consumption  $q_1$ , and a diffusion coefficient  $D_{i1}$ , while the other is characterized by corresponding values  $q_2$  and  $D_{i2}$ . Since we are interested in the *average* value of  $c_2 - c_1$ , we may calculate that average value by using equation (8), in which we put for  $q$  and  $D_i$  some average values  $\bar{q}$  and  $\bar{D}_i$ .

An open shell, such as shown in cross section on Figure 1 may be considered as a closed one, in which a part  $2\pi r^2(1 - \cos \phi)$  is characterized by the values  $q$  and  $D_i$ , while the other part is characterized by values 0 and  $D_e$ . Then we have  $\bar{q} = q(1 - \cos \phi)/2$  and

$$\bar{D}_i = [D_i(1 - \cos \phi) + D_e(1 + \cos \phi)]/2.$$

Introducing those expressions into equation (8) of this paper and the latter into equation (11) of *loc. cit.*, we shall find that  $p$  now contains a factor

$$\frac{1 - \cos \phi}{D_i(1 - \cos \phi) + D_e(1 + \cos \phi)} \quad (9)$$

Instead of equation (4) we now have an equation of the form:

$$\frac{d\phi}{dt} = \frac{A_1 \sin \phi}{\sqrt{1 - \cos \phi} [D_i(1 - \cos \phi) + D_e(1 + \cos \phi)]}. \quad (10)$$

Equation (10) gives, when integrated,

$$\frac{D_e - D_i}{D_i} \sin x + \frac{1}{2} \log \frac{1 + \sin x}{1 - \sin x} = B_1 t + C, \quad (11)$$

where again  $x = \phi/2$ .

Such equations may describe approximately the closure of a half blastula, as has been suggested (Rashevsky, 1940 a). A similar mechanism may be responsible for the invagination of a gastrula. In the latter case things are complicated by the circumstance that the invagination of the entodermal cell layer is necessarily accompanied by a deformation of the ectodermal layer, and the simple equation (1) will therefore not hold. If we assume however that at the time of gastrulation the actual polarization forces in the ectoderm are much smaller than in the entoderm, then approximately, the effect of the ectoderm, which in this case is merely passively "dragged", will be to decrease the right hand side of (1), or in other words to reduce  $B$  or  $B_1$ .

It may also be questioned as to whether considerations about "induced polarization", which lead to equation (11) can be applied at all to an invaginating gastrula. A somewhat similar situation may however arise, when a substance produced by the ectoderm is con-

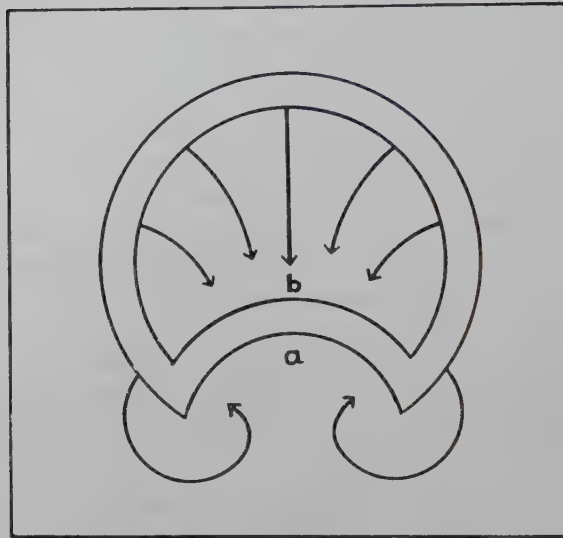


FIGURE 2

sumed by the entoderm, resulting in a flow as shown schematically on Figure 2. The concentration at  $a$  would be less than at  $b$ , producing a polarization which is a function of  $\phi$ . Such an assumption does not seem implausible at all in view of J. Brachet's (1934) findings, that gastrulation can go on in absence of oxygen, which is the only substance with negative metabolism, used in an early embryo in quantities sufficient to produce appreciable mechanical forces. A transport of a substance within the embryo, as shown on Figure 2, would account for such a situation.

On the closure of half blastulae no quantitative data are yet available. Very meager data are available on gastrulation. We shall apply equations (7) and (11) to those data, mainly to *illustrate* a possible quantitative approach to embryological problems.

One characteristic difficulty arises in this connection. Whereas the equations are derived under the assumption that the cellular shell remains spherical during the process of deformation, sections of invaginating gastrula show that those deviate very much from a sphere. This difficulty may be overcome in the following way.

Denoting the total length of the inner periphery of the meridional cross section by  $s$  — in other words, putting  $s = 2AO'$  in Figure 1 — we have

$$s = 2\phi r. \quad (12)$$

Putting  $l = 2r'$ , we find from equation (12) and the second equation (2):



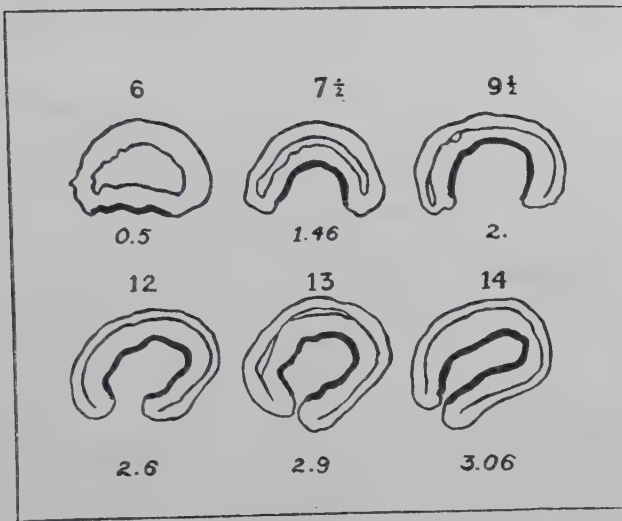


FIGURE 3

$$\frac{l}{s} = \frac{\sin \phi}{\phi}. \quad (13)$$

If the shell, represented on Figure 1 is deformed without stretching or volume change, then it may become rather irregular in shape, and the notion of the angle  $\phi$  will lose its meaning. However the ratio  $l/s$  will remain unchanged, as long as the opening of the shell remains approximately circular.

Considering therefore an actual cellular shell, whose opening is approximately circular, but whose meridional cross section is *not* circular, we may define a quantity  $\phi$  as the root of the transcendental equation (13). To the extent that our simplifying assumptions hold, we may expect this quantity  $\phi$  to follow approximately either equation (7) or (11).

On Figure 3 are shown tracings of meridional cross sections of six different stages of *Amphioxus*, taken from a paper E. G. Conklin (1932, plate 13). The inner perimeters of the cross section of the entoderm, which are shown on Figure 2 in somewhat heavier lines, were measured with a map measure. The dimensions of Figure 2 are considerably reduced, compared with the original. The wheel of the map measure was run over the same perimeter 10 times, without resetting to zero, and the final reading divided by 10. The distances between the ends of the heavier lines were taken as values of  $l$ . The computed values of  $\phi$  for each stage are given in radians underneath each

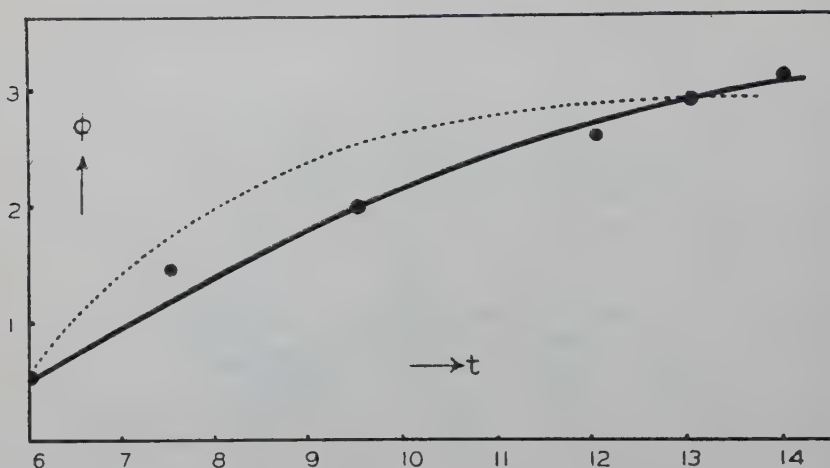


FIGURE 4

section. Above each section is given the time in hours, taken from Conklin's paper.

The simplest check of our equations would be to plot the left hand sides of equation (7) or (11) against  $t$ ; this should give us a straight line. This method however is too sensitive for such inaccurate data as we have. In the neighborhood of  $\phi = \pi$ , that is for the later stages, an error of 8% in the value of  $\phi$  results in an error of 100% in the value of the left hand sides of (7) or (11).

Therefore experimental values of  $t$  were plotted directly against  $\phi$ , and the plots turned by  $90^\circ$ , so as to give  $\phi$  against  $t$ . The results are shown on Figure 4, the dotted line representing equation (7), while the full line represents equation (11). The agreement of the latter with the experimental values is fair. The value of  $(D_e - D_i)/D_i$ , was taken as 1.04.

It must be once more emphasized, that no definite conclusion can be drawn yet from such a comparison, in view of the paucity of the data. But such considerations are very important in principle, since they show a way to new quantitative measurements in embryology.

If instead of five different stages, we had fifteen, and if for *each* stage we had a large number of cross sections, so that accurate *average* values of  $\phi$  could be calculated, a comparison of theory and experiment would become very meaningful. It must be remarked that in general the quantity  $p$  in equation (1) may be a function of  $\phi$  and of  $t$  explicitly (Rashevsky, 1940 a, 1940 b). If  $d\phi/dt$  is given experimentally we may determine from equation (4), by means of equation (3), the functional relation between  $p$  and  $\phi$  or  $t$ .

The author is indebted to Mr. H. D. Landahl for checking the calculations.

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## SOME CONSIDERATIONS ON MATHEMATICAL MOLECULAR BIOPHYSICS

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The possibility of a single molecule or of a few molecules controlling the basic metabolic reactions in a cell is discussed from the molecular-kinetic point of view. For such a control by a single molecule to be possible, it is necessary to assume a chain reaction, consisting of at least two steps.

Hitherto the development of mathematical biophysics has been based almost exclusively on "macroscopic" concepts of classical physics. Diffusion phenomena, plastic deformations, and other phenomena important for mathematical biophysics, are treated from the point of view of a continuum. Different metabolic reactions are considered as given, and although definite assumptions are made and studied about the interrelations of such reactions, nevertheless these assumptions are of such a nature as not to involve any molecular or atomic considerations.

It is very significant that even with this limitation to the domain of the classical physics of the continuum, mathematical biophysics has made considerable progress in quantitatively describing a large array of biological phenomena. Nevertheless it has been clear from the very beginning of mathematical biophysics, that eventually an extension into the domain of molecular or atomic physics will have to be made (Rashevsky, 1934). Even long before the development of mathematical biophysics proper, a number of biological observations have been pointing to the importance for biology of atomic physics, and have turned the attention of noted quantum physicists to biological phenomena (Jordan, 1939). Observations on the killing of unicellular organisms by different radiations indicate that sometimes a single *X-ray* quantum, or a single  $\alpha$ -particle hitting a cell are capable of causing its death. Although for a biologist even a large cell is still a "microscopic" object, from the point of view of molecular physics an average cell is decidedly "matter in bulk", and at first sight it might look puzzling as to how a single molecule coming from outside can totally upset a mechanism composed of some  $10^{14}$  other molecules, a

mechanism known to follow in many respects the laws of the physics of the continuum.

Another set of biological facts, falling into a similar category is supplied by observations on the extreme sensitivity of some sense organs, particularly that of smell. The number of molecules leaving some solid aromatic substances is very small in itself. If we consider the amazing sensitivity of the sense of smell of some animals, we may wonder whether only a few molecules may not be responsible here for setting into operation a complex macroscopic mechanism of sensation.

A still different field of biology leading us to the same questions is the study of some vitamins and hormones. Even now in many cases biological tests are the only ones that are sensitive enough to reveal the presence of those substances, the most refined physicochemical methods still failing. The more or less tacit assumption is frequently made, that surface action may account for the strong activities of small quantities of such substances, a very small volume concentration being sufficient to form monomolecular surface layers, which affect the surface properties of cells. In some cases however, a simple calculation shows that the concentrations of the active substances are so small, as to be quite insufficient to cover any appreciable area of a cell surface.

Phenomena of immunization, sensitization and allergy also raise questions of the same kind.

It is therefore indicated to investigate first in its general aspects the problem of how such effects may be brought about, and to ask ourselves whether such phenomena do present any particular difficulties from the point of view of molecular kinetics.

The problem consists of two parts. First there is the question of the atomic mechanism of catalytic interactions. To this field some contributions have already been made by quantum mechanics, and important further progress is undoubtedly still to come. Second — there is the purely kinetic problem, as to the conditions permitting the above mentioned atomic mechanism to come into action. In order for a molecule  $A$  to affect catalytically other molecules  $B_1, B_2 \dots$  etc., it is necessary that a relatively close contact between the molecule  $A$  and the molecules  $B_1, B_2 \dots$  etc. should be established for at least a short time. All atomic forces, decrease very rapidly with increasing distance, and any distant actions are out of question.

Consider, for the sake of definiteness, a reaction in which a molecule  $B$  breaks up into molecules  $C$  and  $D$ . Let the rate of breakdown of  $B$  be  $q \text{ gm} \cdot \text{cm}^{-3} \text{ sec}^{-1}$ . Denoting the molecular weight of  $B$  by  $M$ , Avogadro's number by  $N$  and the volume of the cell by  $V$ , we find that

$$qNV/M \quad (1)$$

molecules per cell per second are broken up. Suppose that  $n$  molecules  $A$  of a catalyst are present in the cell, catalyzing the breakdown reaction. Then each molecule of the catalyst must collide every second with at least

$$qNV/Mn \quad (2)$$

molecules  $B$ .

Let the average concentration of  $B$  in the cell be  $\bar{c}$  gm · cm<sup>-3</sup>, or  $\bar{c}N/M$  molecules per cm<sup>3</sup>. Considering dilute solutions, in which the molecules behave like those of an ideal gas, denoting by  $\sigma_1$  and  $\sigma_2$  the radii of the molecules  $A$  and  $B$  respectively, and by  $v_1$  and  $v_2$  their respective average thermal velocities and putting

$$\sigma = \frac{\sigma_1 + \sigma_2}{2}, \quad (3)$$

we have approximately (Jaeger, 1926) for the number  $Z$  of collisions which one molecule  $A$  makes with molecules  $B$ , the expression:

$$Z = \frac{3v_2^2 + v_1^2}{3v_2} \frac{\pi \bar{c} N \sigma^2}{M}. \quad (4)$$

Expression (4) holds for  $v_2 > v_1$ , which is equivalent to the assumption that the molecule  $A$  is heavier than  $B$ . This is the more plausible case. When  $v_2 < v_1$ , the quantities  $v_1$  and  $v_2$  have to be interchanged in equation (4). (Jaeger, 1926).

The presence of the solvent will affect the number  $Z$ , but will not change its order of magnitude much (Jaeger, 1926).

In order that the  $n$  molecules  $A$  could maintain the necessary rate of reaction  $q$ , it is necessary that  $Z$  should be at least equal to or larger than the expression (2). In other words, putting

$$\frac{3v_2^2 + v_1^2}{3v_2} = v, \quad (5)$$

we must have

$$v\pi\bar{c}\sigma^2n \geq qV. \quad (6)$$

But (Rashevsky, 1940, p. 21)

$$\bar{c} = c_0 + \Delta q, \quad (7)$$

where  $c_0$  is the external concentration of the metabolite  $B$ , and  $\Delta$  is a quantity determined by the size of the cell, its permeability to  $B$  and the diffusion coefficient of  $B$  in the cell. Equations (6) and (7) give

$$\Lambda \geq \frac{V}{\pi v \sigma^2 n} - \frac{c_0}{q} . \quad (8)$$

Considering metabolic reactions with a high rate, such as the respiratory reactions, we have  $-q \approx 10^{-6}$  gm cm<sup>-3</sup> sec<sup>-1</sup>. The quantity  $v$  is of the order of  $10^4$  cm sec<sup>-1</sup>;  $c_0$  is about  $10^{-5}$  gm cm<sup>-3</sup>, and for an average cell  $V \approx 10^{-7}$  cm<sup>3</sup>. Taking  $\sigma \approx 10^{-8}$  cm, and putting  $n = 1$ , we find from expression (8):

$$\Lambda \geq 10^4 \text{ sec.} \quad (9)$$

Such a value of  $\Lambda$ , although physically quite possible, is absurd for such values of  $q$  as we have assumed. It would make  $\bar{c}$  negative, since  $q < 0$ .

If we consider the similar case of a substance  $B$  produced, then such a value of  $\Lambda$  will mean  $\bar{c} \approx 10^{-2}$  gm cm<sup>-3</sup>, which is also too high. The values of  $\Lambda$  for different respiratory metabolites are of the order of magnitude of a few seconds (Rashevsky 1940). In order to satisfy relation (8) under those conditions, we should have  $n \approx 10^4$ . This still represents an exceedingly low concentration of the catalyst, corresponding, for molecular weights of the order of one hundred, to  $10^{-10}$  gm · cm<sup>-3</sup>. A single molecule however could not control the whole reaction in this case.

Consider however a more complicated scheme. Let the reaction considered here, and going at a rate of  $10^{-6}$  gm cm<sup>-3</sup> sec be controlled by a catalyst, present in a concentration  $\bar{c}_c = 10^{-10}$  gm cm<sup>-3</sup>, sufficient for the purpose. Let, however, this concentration  $\bar{c}_c$  be determined by the material balance between the rate of production of the catalyst  $A_c$  and its rate of diffusion from the cell. Let the rate  $q_c$  of production of  $A_c$  be very small, and its external concentration be zero. In that case the condition that the production of  $A_c$  would be controlled by a single molecule  $A$  would again require that  $\Lambda_c$ , the value of  $\Lambda$  for the substance  $A_c$ , should be of the order of  $10^4$  sec. This would require a very low permeability and diffusion coefficient for  $A_c$ . If  $q_c = 10^{-15}$  gm cm<sup>-3</sup> sec., this will just give the correct value for  $\bar{c}_c$ .

It is thus possible for a single molecule in a cell to control a reaction going on at a rate of  $10^{-6}$  gm cm<sup>-3</sup> sec<sup>-1</sup>, and involving concentrations of  $10^{-5}$  gm cm<sup>-3</sup>. But this control must be made through at least one intermediate stage. The single molecule  $A$  controls the formation of  $A_c$ , which goes on at a very small rate ( $10^{-15}$  gm cm<sup>-3</sup> sec<sup>-1</sup>) and is present in small concentrations ( $10^{-10}$  gm cm<sup>-3</sup>). The substance  $A_c$  in its turn controls the rate of reaction of  $B$ . When the "master molecule"  $A$  is destroyed, the reaction  $B$  stops due to the disappearance of  $A_c$ . The concentration of the latter however will decrease exponentially, with time, and the time lag between the destruc-



tion of the molecule  $A$  and the cessation of reaction  $B$  will be of the order of  $\Lambda_c$ , that is of the order of hours (Rashevsky 1940). This time-lag will vary as the volume of the cell. For small bacteria with  $V \sim 10^{-11} \text{ cm}^3$ , that time lag may be reduced to only a few seconds. The assumption of a rather large size  $\sigma_1$  for the master molecule  $A$ , will also reduce  $\Lambda_c$ .

The author is indebted to Mr. H. D. Landahl for a discussion and check of calculations.

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## ERRATA

In the paper "Nerve Conduction Theory: Some Mathematical Consequences of Bernstein's Model" by F. Offner, A. Weinberg, and G. Young, pp. 89-103, replace  $s$  and  $s_0$  by  $1/s$  and  $1/s_0$ , respectively, on page 98, line 32 and on page 99, line 21; replace  $V$  by  $V'$  on page 101, line 7. Equation (24), page 99 should read

$$v = k\sqrt{f(d) \times d/F(d)}$$





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